

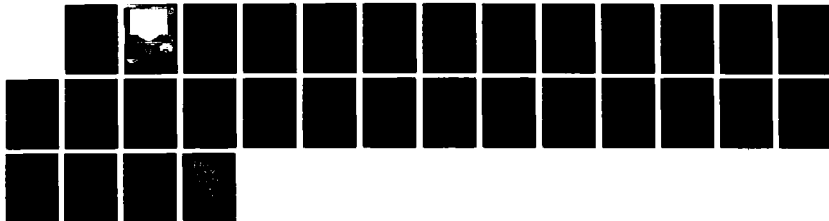
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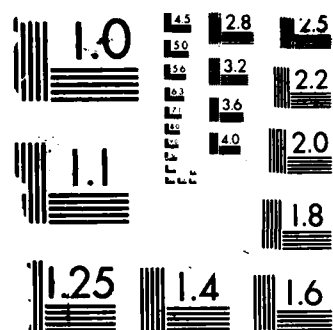
A TRANSFORMATION/WEIGHTING MODEL FOR ESTIMATING
MICHAELIS-MENTEN PARAMETE. (U) NORTH CAROLINA UNIV AT
CHAPEL HILL INST OF STATISTICS R J CARROLL ET AL.
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A TRANSFORMATION/WEIGHTING MODEL FOR
ESTIMATING MICHAELIS-MENTEN PARAMETERS

Raymond J. Carroll

Noel Cressie

David Ruppert

Raymond J. Carroll and David Ruppert are with the Department of Statistics, the University of North Carolina at Chapel Hill, Chapel Hill, NC 27514. Noel Cressie is with the Department of Statistics at Iowa State University, Ames, Iowa 50011. Carroll's research was supported by the Air Force Office of Scientific Research Contract AFOSR F 49620 85 C 0144. Ruppert's research was supported by the National Science Foundation Grant MCS 8100748. The authors thank Perry Haaland for helpful conversations.

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ABSTRACT

There has been considerable disagreement about how best to estimate the parameters in Michaelis-Menten models. ^{They point out} We point out that many fitting methods are based on different stochastic models, being weighted least squares estimates after appropriate transformation. ^{The latter} We propose a flexible model which can be used to help determine the proper transformation and choice of weights. The method is illustrated by examples. ^(Example 1)

^{nonlinear regression; Lineweaver Burk transformation}

SECTION 1 : Introduction

The Michaelis-Menten relation between a response y and a predictor x can be written as

$$(1.1) \quad y = Vx/(K+x) = \{\alpha_0 + \alpha_1/x\}^{-1} ,$$

where $\alpha_0 = 1/V$ and $\alpha_1 = K/V$. The model applies at least approximately in a variety of biological and biochemical situations, see Cressie & Keightley (1981), Currie (1982), Johansen (1984) and Ruppert & Carroll (1985). In fisheries research, (1.1) is called the Beverton-Holt (1957) spawner-recruit model.

There is considerable debate as to how one can best estimate the parameters in model (1.1). The simplest method is to linearize (1.1) by the double reciprocal or Lineweaver-Burke transformation :

$$(1.2) \quad 1/y = \alpha_0 + \alpha_1/x ,$$

and then regress $1/y$ on $1/x$ using least squares to estimate (α_0, α_1) . While the Lineweaver-Burke model is often used, in some areas it is thought to be a particularly poor fitting technique. Currie (1982) states that the estimates from this technique are "more prone to be biased" than are the estimates from "any other commonly used technique". Other authors have come to the same conclusion, based in part on a study by Dowd & Riggs (1965).

A second common method is the Woolf linearizing transformation, which multiplies through by x in (1.2), leading to the model

$$(1.3) \quad x/y = \alpha_1 + \alpha_0 x .$$

Cressie & Keightley (1981) find that for hormone-receptor assays, least squares applied after the Woolf transformation is more robust to outlying points than is least squares after the Lineweaver-Burke transformation, although when using a robust fit the latter was marginally better. For this and other reasons (Keightley, Fisher & Cressie, 1983), they prefer the Woolf transformation for analyzing hormone-receptor assays.

Currie (1982) recommends fitting (1.1) directly by nonlinear least squares. He also states that "The Woolf transformation, the best among the linearizing transformations, ... provides unreliable parameter estimates ... (linearizing) transformations should not be used", although he adds the qualifying statement "except in cases where they stabilize the error".

It seems to us that the proper fitting method necessarily depends on the particular subject area, experiment and underlying distribution. No general conclusions about a fitting method can or should be made without taking these considerations into account. Fitting (1.1) - (1.3) by unweighted least squares should be seen as a consequence of fitting different stochastic models for the data. If ϵ has mean zero and variance one, fitting (1.1) - (1.3) is a consequence of assuming, respectively

$$(1.4) \quad \text{Nonlinear (Currie)} : \quad y = \{\alpha_0 + \alpha_1/x\}^{-1} + \sigma\epsilon ;$$

$$(1.5) \quad \text{Lineweaver-Burke} : \quad y = \{\alpha_0 + \alpha_1/x + \sigma\epsilon\}^{-1} ;$$

$$(1.6) \quad \text{Woolf} : \quad y = \{\alpha_0 + \alpha_1/x + \sigma\epsilon/x\}^{-1} .$$

That these may be very different stochastic models for data can be seen by letting σ be small and taking a simple Taylor series expansion. If $E(y)$ and

SD(y) denote the mean and standard deviation of y, we have the following approximations :

<u>Nonlinear</u> :	$SD(y) \approx \sigma$;
<u>Lineweaver-Burke</u> :	$SD(y) \approx \sigma \{E(y)\}^2$;
<u>Woelf</u> :	$SD(y) \approx \sigma \{E(y)\}^2 / x$.

Surely it should come as no surprise that if one runs a simulation in which the errors in (1.1) are additive or nearly so, then ordinary nonlinear least squares should be a clear winner over linearizing transformations, with the Woelf transformation second and Lineweaver-Burke a poor third. Yet this is essentially what Currie did in his study. We have little doubt that had he based his simulation on the underlying distribution implied by say the Woelf model, then he would have found that linearizing is the method of choice.

Storer, Darlison & Cornish-Bowden (1975) present real-life examples for which the standard deviation of y appears to be proportional to the mean or a power of the mean. This evidence with real data suggests that one should take care to study the underlying distributional properties of an experiment, and not assume that the Nonlinear model holds in all situations.

The three models (1.4) - (1.6) are special cases of a simple generalization to the Transform Both Sides approach of Carroll & Ruppert (1984, 1987a, 1987b), see also Bates, Wolf & Watts (1985) and Snee (1986) for nice applications of this technique. Define the usual Box - Cox (1964) power transformations :

$$v^{(\lambda)} = (v^\lambda - 1) / \lambda \quad \text{for } \lambda \neq 0 ;$$

$$v^{(\lambda)} = \log(v) \quad \text{for } \lambda = 0 .$$

The Extended Transform Both Sides Michaelis-Menten Model is

$$(1.7) \quad y^{(\lambda)} = \{ (\alpha_0 + \alpha_1/x)^{-1} \}^{(\lambda)} + \sigma x^\theta \epsilon.$$

See Carroll & Ruppert (1987a) for an introduction to this model. By choosing $\lambda = 1$ and $\theta = 0$, we obtain the nonlinear model (1.4). The Lineweaver-Burke model (1.5) sets $\lambda = -1$, $\theta = 0$, while the Woolf model (1.6) sets $\lambda = \theta = -1$.

The purpose of this paper is to illustrate the use of the Extended Transform Both Sides Model (1.7). In section 2, we discuss properties of the model and methods of fitting it. In section 3, we present examples.

An alternative method of estimation due to Cornish-Bowden & Eisenthal is discussed by Dalgaard & Johansen (1986). We do not study this method because as they state "it ... appears dangerous to us to use these estimates without making a careful investigation of the error distributions, and if one can do that, it would appear more reasonable to apply the model based maximum likelihood estimator".

SECTION 2 : The Extended Transform Both Sides Model

We consider a slight generalization of model (1.7), one which permits any nonlinear regression model and a wider variety of models for the standard deviation :

$$(2.1) \quad y^{(\lambda)} = f(x, \beta)^{(\lambda)} + \sigma g(x, \theta) \epsilon.$$

Here $f(x, \beta)$ is called the regression function, $g(x, \theta)$ is called the standard deviation function and (λ, β, θ) are unknown parameters which are to be estimated. In accordance with tradition, ϵ is assumed to be approximately normally distributed with mean zero and variance one. In (2.1), the standard deviations could also depend on the mean, but we do not discuss this refinement here.

To make the identifications with (1.7), we have

$$\beta = (\alpha_0, \alpha_1) : f(x, \beta) = \{\alpha_0 + \alpha_1/x\}^{-1} : g(x, \theta) = x^\theta.$$

Assuming only symmetry of ϵ , under this model y has median $f(x, \beta)$ independent of the values of λ and θ . Snee (1986) has argued that for heavily skewed data in nonlinear regression, it is more natural to model the median rather than the mean, with the transformation taking care of skewness and some of the heteroscedasticity in the data. Alternatively to (2.1), one might choose to model the mean-variance relationship directly, i.e., build a heteroscedastic nonlinear regression model without transformation. As an approximation when σ is small, the two approaches are closely related. In this instance, the mean and median nearly coincide, skewness is not a great

issue and y has approximate standard deviation $\sigma g(x, \theta) f(x, \beta)^{1-\lambda}$. Hence, a natural alternative to the Extended Transform Both Sides Model is the heteroscedastic model

$$E(y) = f(x, \beta) ;$$

(2.2)

$$SD(y) = \sigma g(x, \theta) f(x, \beta)^{1-\lambda}.$$

Methods for fitting model (2.2) are discussed by Davidian & Carroll (1986) and Carroll & Ruppert (1987a, Chapters 2 and 3). The approximate model (2.2) offers some insight when $g(x, \theta) = x^\theta$. In many of these problems $f(x, \beta)$ given by (1.1) is approximately proportional to a power of x , so that θ and λ will be difficult to distinguish. In most of the examples we have studied, we have found confidence regions for (λ, θ) to be fairly broad, but not so broad as to include all three of the Nonlinear, Woolf and Lineweaver-Burke models simultaneously.

Assuming the transformation achieves approximate normality, the loglikelihood for model (2.1) is given by

$$\begin{aligned} \ell(\lambda, \theta, \beta, \sigma) = & \sum_{i=1}^N \left[(\lambda-1) \log(y_i) - \log\{\sigma g(x_i, \theta)\} \right] \\ & - \sum_{i=1}^N \left[\{y_i^{(\lambda)} - f(x_i, \beta)^{(\lambda)}\} / g(x_i, \theta) \right]^2 / \{2\sigma^2\} . \end{aligned}$$

For given values of (λ, θ) , β and σ can be estimated by weighted nonlinear least squares regression of $y_i^{(\lambda)}$ on $f(x_i, \beta)^{(\lambda)}$ with weights $1/g^2(x_i, \theta)$. If the weighted mean squared error is denoted by $\hat{\sigma}^2(\lambda, \theta)$, we thus obtain the

maximized loglikelihood

$$(2.3) \quad \ell_{\max}(\lambda, \theta) = \sum_{i=1}^N \left[(\lambda-1) \log(y_i) - \log\{\hat{\sigma}(\lambda, \theta) g(x_i, \theta)\} \right].$$

The maximum likelihood estimates of λ and θ can be computed by maximizing (2.3). In the Michaelis-Menten model, we usually restrict $-1 \leq \lambda, \theta \leq 1$, and compute (2.3) over a grid of values. This enables us to plot the loglikelihood surface, and as a simple by-product make tests for the fit of the Nonlinear model ($\lambda=1, \theta=0$), the Woolf model ($\lambda=\theta=-1$) and the Lineweaver-Burke model ($\lambda=-1, \theta=0$). Such computation is usually very quickly done. In the examples of the next section, using a grid size of 0.05 and the matrix programming language GAUSS on an IBM PC/AT, the loglikelihood surface took less than 5 minutes to compute.

For more complex regression and standard deviation functions, one can maximize the likelihood in all the parameters simultaneously either by a general maximum likelihood program or by using nonlinear least squares programs. Let y_m and $g_m(\theta)$ be the geometric means of $\{y_i\}$ and $\{g(x_i, \theta)\}$ respectively. Define

$$D_i(\lambda, \theta, \beta) = g_m(\theta) y_m^{1-\lambda} \left[\{y_i^{(\lambda)} - f(x_i, \beta)^{(\lambda)}\} / g(x_i, \theta) \right].$$

Then the maximum likelihood estimates of (λ, θ, β) minimize the sum of squares

$$\sum_{i=1}^N D_i^2(\lambda, \theta, \beta).$$

To use a nonlinear least squares program to make this computation, identify

$D_i(\lambda, \theta, \beta)$ as the "regression function" and identify all "responses" to be zero; see Carroll & Ruppert (1987a, Chapter 5).

Professor D. Bates (personal communication) has suggested that it is useful to plot the individual components of β as a function of (λ, θ) , as a check on the sensitivity of the parameter estimates to the choice of the model.

As argued in Carroll & Ruppert (1984), the effect on the distribution of $\hat{\beta}$ due to estimating (λ, θ) is often small. In practice, we have sometimes found it useful to adjust standard residuals for leverage, see Cook & Weisberg (1982). For robust estimation and diagnostics in this type of model, see Carroll & Ruppert (1987a, Chapter 6) and (1987b).

SECTION 3 : Examples

In this section, we analyze two data sets. The analyses are meant to be illustrative numerical examples rather than complete investigations.

EXAMPLE 3.1 : Skeena River Sockeye Salmon

The data in Table 1, taken from Ricker & Smith (1975), concern the relationship between x = number of spawners and y = total return or number of recruits for Skeena River Sockeye Salmon. The data are given for the years 1940 - 1967. Since our intention is to provide numerical illustrations only, we have deleted 1951 which was affected by a rockslide and 1955 because other analyses indicate that it is rather extreme. A possibility which we will not consider is that of dependencies in the data. For alternative analyses including robust methods and influence diagnostics and different models, see Carroll & Ruppert (1987a, 1987b).

The studentized residuals from the Woolf model, while not pictured here to conserve space, suggest a systematic lack of fit and/or severe heteroscedasticity. The Spearman rank correlation between the absolute studentized residuals and the predicted values is 0.60 with a formally computed significance level of 0.001. The studentized residuals from the Nonlinear model suggest a clear pattern of classic heteroscedasticity; see Figure 1. Some idea of the severity of the problem can be gleaned from the fact that the Spearman rank correlation is 0.50 with a formal significance level of 0.007. The Lineweaver-Burke studentized residuals show no such pattern of obvious heteroscedasticity, but they do seem skewed; see Figure 2.

Model (1.7) was fit to the data and the maximum likelihood estimates for

(λ, θ) are (0.34, 0.77). The likelihood ratio χ^2 test statistic based on two degrees of freedom is $\chi^2 = 10.7$ for the Nonlinear model ($\lambda=1, \theta=0$), $\chi^2 = 18.5$ for the Woolf model ($\lambda=\theta=-1$) and $\chi^2 = 8.43$ for the Lineweaver-Burke model ($\lambda=-1, \theta=0$), these having significance levels of 0.005, 0.0001, and 0.015 respectively. The likelihood ratio tests agree with our graphs in concluding that none of the three standard models have constant variance with approximately normally distributed errors.

Of course, no choice of (λ, θ) perfectly explains skewness and heteroscedasticity in these data. However, $\lambda = \theta = .5$, ($\chi^2 = 1.14$) and $\lambda = \theta = 1$ ($\chi^2 = 2.24$) both seem adequate. The choice $\lambda = \theta = 1$, for which the residual plot is given in Figure 3, has the feature that it is a model of heteroscedasticity without data transformation, which some will find to be an advantage. In this model, the standard deviation is proportional to the number of spawners, which changes by a factor of about 4 over the observed data. Alternatively, one might model the variance as proportional to a power of the mean, see Carroll & Ruppert (1987a, Chapter 3 and example 6.4.1).

EXAMPLE 3.2 : A Hormone Receptor Assay

In Table 2 we list the results of a small hormone-receptor assay as taken from Cressie & Keightley (1979, Table 3); the ordering is slightly different to reflect the fact that there were duplicates at six levels. Our purpose is to illustrate the application of Extended Transform Both Sides, but not to give a complete analysis. Indeed, the data set is very small (only 12 observations), and it would be unwise to read too much into the analysis.

The estimates of (λ, θ) were constrained to lie in the unit square, i.e., $-1 \leq \lambda, \theta \leq 1$. The maximum likelihood estimate occurs very near the Lineweaver-Burke model, being $\hat{\lambda} = -1.0$ and $\hat{\theta} = -0.1$. The χ^2 test statistic for the Lineweaver-Burke model ($\lambda = -1.0, \theta = 0$) is $\chi^2 = 0.78$, for the Woolf model ($\lambda = -1.0, \theta = -1.0$) it is $\chi^2 = 8.29$, while it is $\chi^2 = 4.54$ for the Nonlinear model ($\lambda = 1.0, \theta = 0$). Even though the confidence region is fairly large, the Extended Transform Both Sides model suggests that the Woolf and (to a lesser extent) the Nonlinear models might provide a worse fit than does Lineweaver-Burke.

In Figures 4 - 6 we plot the studentized residuals from the Woolf, Nonlinear and Lineweaver-Burke fits against the logarithm of the predicted values. We have also looked at plots of the absolute studentized residuals. To our eye, as suggested by the likelihood analysis, the Lineweaver-Burke model seems to do the best job of accounting for heterogeneity of variance. There are additional factors of some interest. First, the Spearman rank correlation of absolute studentized residuals against their predicted values is .44, .17 and -.32 for the Woolf, Nonlinear and Lineweaver-Burke models respectively. This might suggest that the Lineweaver-Burke model has

overcorrected for heterogeneity of variance. Note too that the plots suggest that there may be both within and between components of variance, which we have not been attempting to model.

There is also the issue of robustness and leverage. One can do a robust fit to the data here, but in the interest of space we only do the following analysis. Since the data are essentially collected in pairs, it is of some interest to see if there is a single pair of observations which has a very large effect on the final parameter estimates. In Table 3 we have recomputed the likelihood after deleting successive pairs of data points. What is most striking here is the effect of deleting the first pair of observations. If this pair is deleted, then in terms of likelihood, all three of Lineweaver-Burke, Woolf and the Nonlinear model are essentially equivalent. Either using the full data or keeping the first pair and deleting any of the others leads to a strong preference (in terms of likelihood) for Lineweaver-Burke. This example suggests that especially for small data sets one will need to examine the data carefully to ascertain whether the answers are being driven by a small group of observations.

As a postscript, there is another linearizing transformation ($y/x = \alpha_0 + \alpha_1 y$) yielding the Scatchard model, which has been used heavily in the context of hormone-receptor assays. This model is not a special case of the model (1.7). Its performance on hormone-receptor assay data is shown by Cressie and Keightley (1981) to be markedly inferior to that of either the Woolf or the Lineweaver-Burke models.

SECTION 4 : Discussion

In fitting a Michaelis-Menten model to data, the three standard fitting models are a consequence of different distributions for the responses. It is clear that no single fixed distribution will fit all situations, so it should also be clear that no single fitting technique will be universally appropriate. The proper model and its associated fitting techniques should be allowed to vary among subject areas and even within a subject area.

We view Extended Transform Both Sides as a reasonable, flexible and effective method for helping to decide upon a model for data. The method is easily computed and enables standard model checks to be performed. Naturally, as indicated in section 2, the model is not restricted to Michaelis-Menten relationships. We do not advertise Extended Transform Both Sides as a panacea, nor do we advocate that it be used as a black box. While the technique is widely applicable, no simple model will fit all data sets.

Inferential problems concerning the parameters V and K in the model (1.1) has not been our concern in this article. The validity of Wald-type confidence statements depend on the design and parameterization, see Bates & Watts (1980). For further discussion, see Carroll & Ruppert (1987a, Chapters 2, 4 and 5).

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TABLE 1

Skeena River Sockeye Salmon data. Years 1951 and 1955 have been deleted in the illustrative example of section 3. Data are in millions of fish.

<u>YEAR</u>	<u>SPAWNERS</u>	<u>RECRUITS</u>
1940	0.963	2.215
1941	0.572	1.334
1942	0.305	0.800
1943	0.272	0.438
1944	0.824	3.071
1945	0.940	0.957
1946	0.486	0.934
1947	0.307	0.971
1948	1.066	2.257
1949	0.480	1.451
1950	0.393	0.686
1951	0.176	0.127
1952	0.237	0.700
1953	0.700	1.381
1954	0.511	1.393
1955	0.087	0.363
1956	0.370	0.668
1957	0.448	2.067
1958	0.819	0.644
1959	0.799	1.747
1960	0.273	0.744
1961	0.936	1.087
1962	0.558	1.335
1963	0.597	1.981
1964	0.848	0.627
1965	0.619	1.099
1966	0.397	1.532
1967	0.616	2.086

TABLE 2

Results of a Hormone Receptor Study. Data are in units of fmol/mg cytosolprotein.

<u>X</u>	<u>Y</u>
0.358	1.43
0.358	1.46
0.782	2.23
0.771	2.36
1.725	2.88
1.703	3.15
2.672	3.34
2.680	3.43
3.653	3.58
3.629	3.81
4.630	3.75
4.697	3.57

TABLE 3

Hormone-Receptor Study. The values of the log likelihood for (λ, θ) are listed after successively deleting pairs of points.

Deleted Observations	Woelf	Lineweaver Burke	Nonlinear
(1,2)	19.44	20.42	20.55
(3,4)	19.85	23.57	21.02
(5,6)	20.20	24.70	22.43
(7,8)	18.91	23.23	20.66
(9,10)	22.09	24.05	21.86
(11,12)	20.92	24.05	21.86

Figure 1

The studentized residuals plotted against the logarithm of the predicted values for the Nonlinear model in the Skeena river data set.

Figure 2

The studentized residuals plotted against the logarithm of the predicted values for the Lineweaver-Burke model in the Skeena river data set.

Figure 3

The studentized residuals plotted against the logarithm of the predicted values for the untransformed heteroscedastic model in the Skeena river data set.

Figure 4

The studentized residuals plotted against the logarithm of the predicted values for the Woolf model in the Hormone Receptor Study.

Figure 5

The studentized residuals plotted against the logarithm of the predicted values for the Nonlinear model in the Hormone Receptor Study.

Figure 6

The studentized residuals plotted against the logarithm of the predicted values for the Lineweaver-Burke model in the Hormone Receptor Study.

Figure 1

Skeena River Data
Nonlinear Model

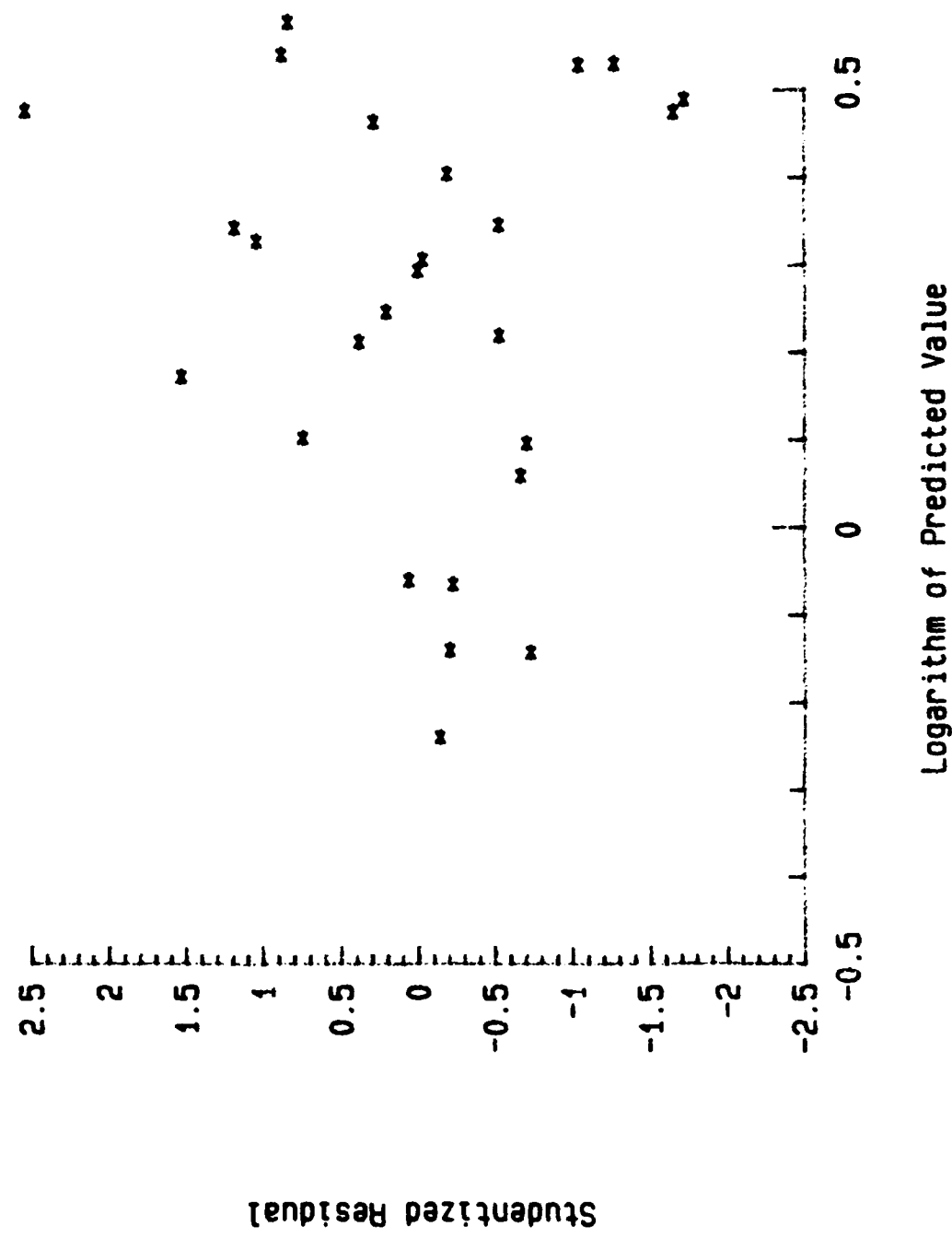


Figure 2

Skeena River Data
Lineweaver Burke Model

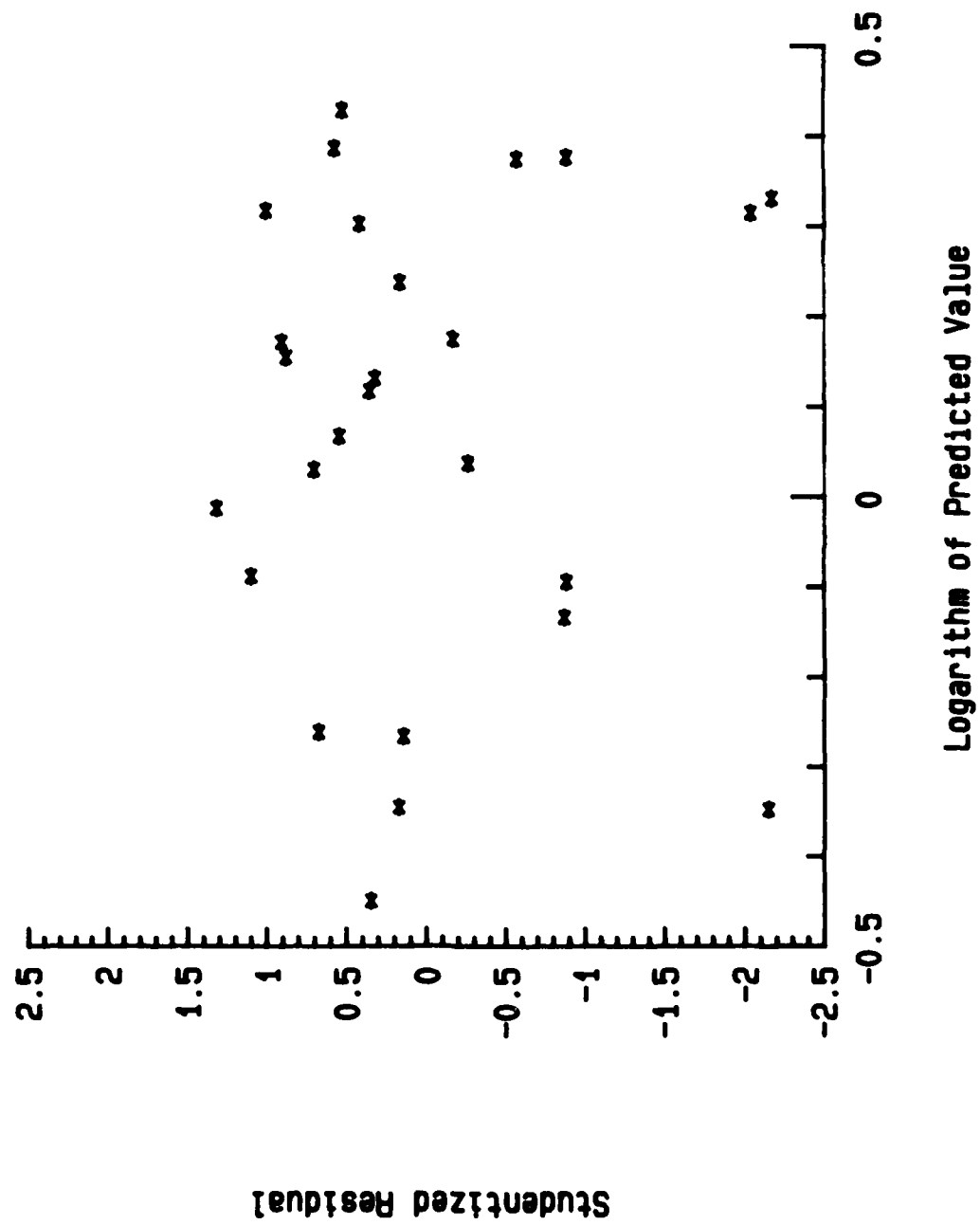


Figure 3

Skeena River Data
Untransformed Heteroscedastic Model

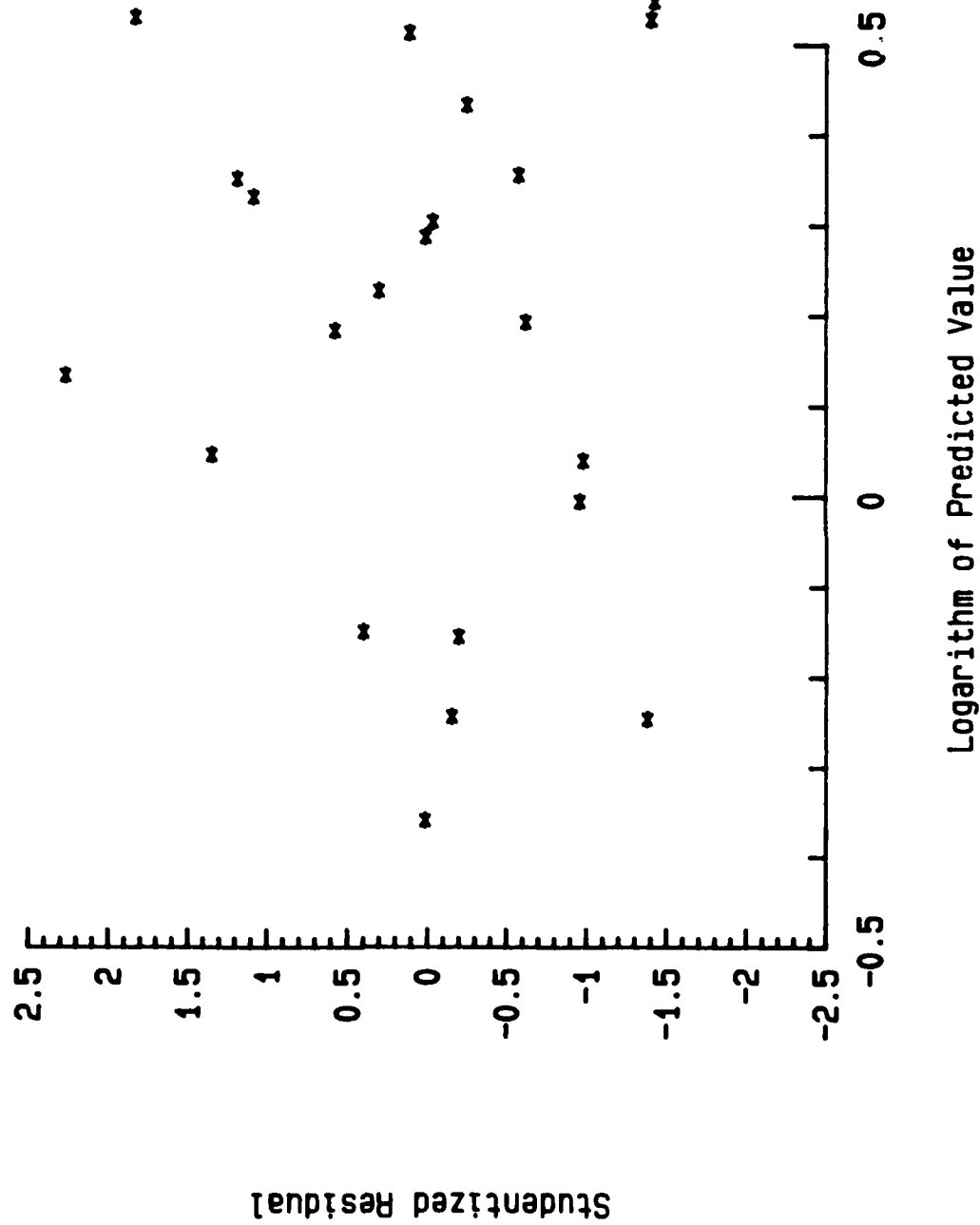


Figure 4

Hormone Receptor Assay
Woolf Model

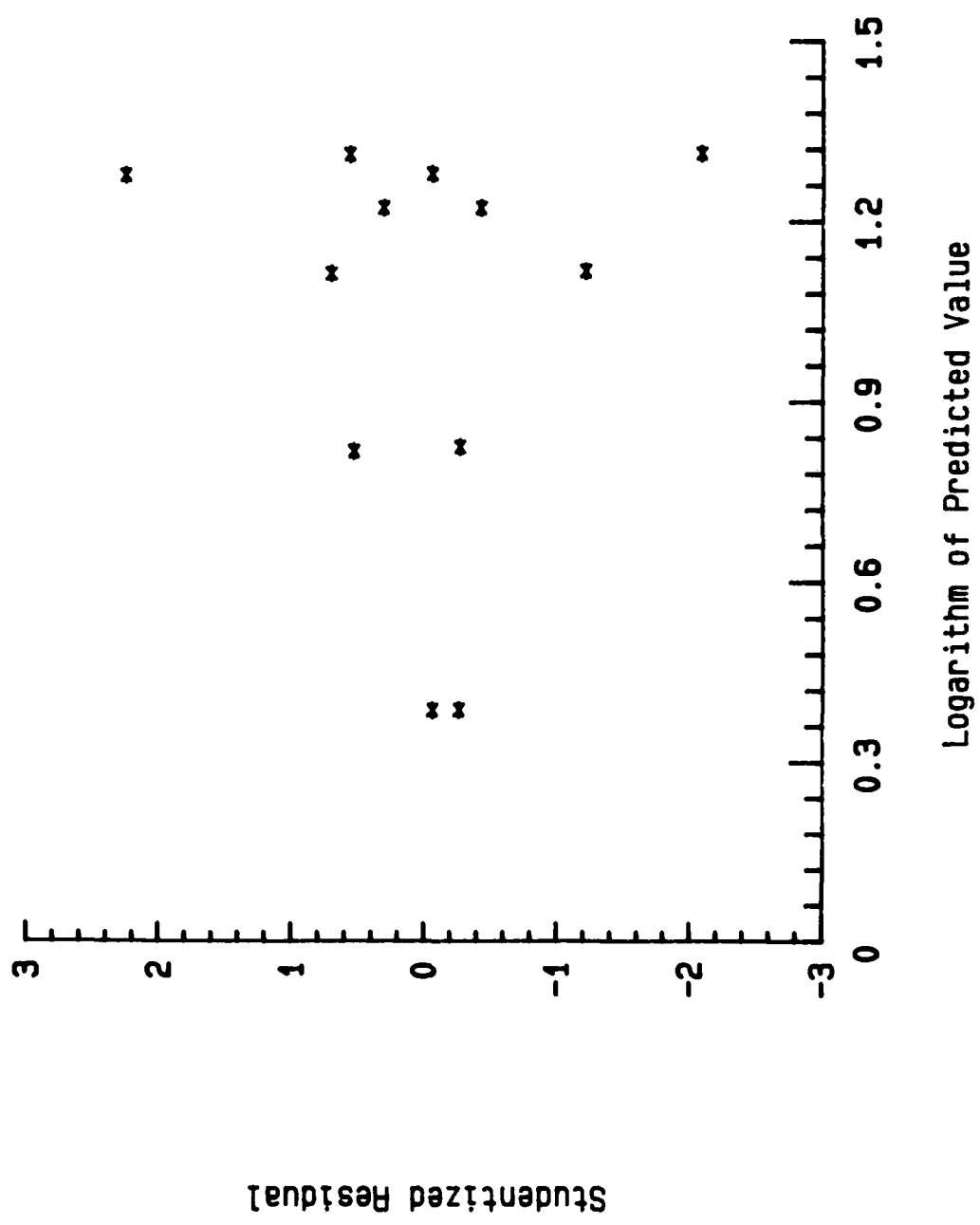
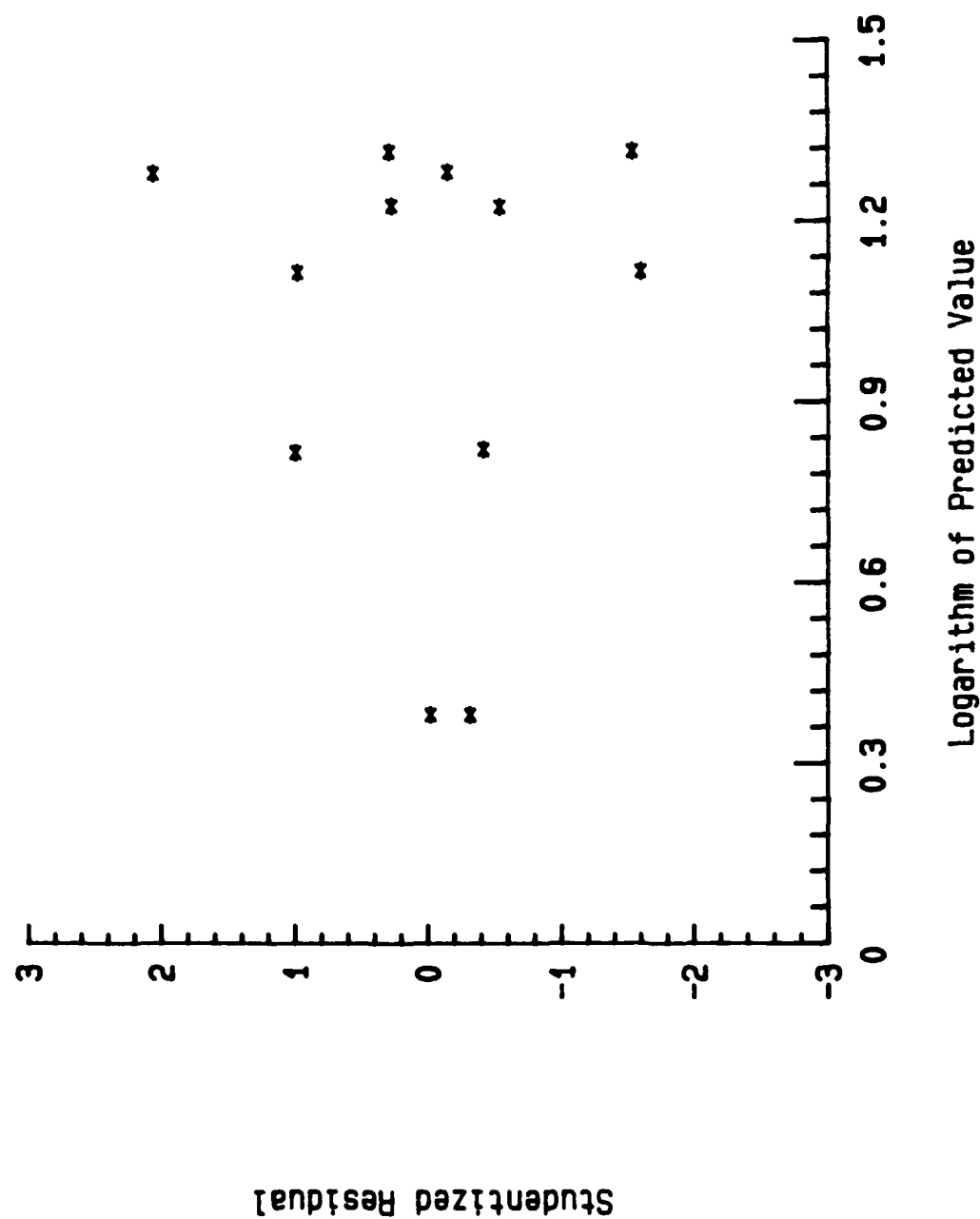


Figure 5

Hormone Receptor Assay
Nonlinear Model



Hormone Receptor Assay
Lineweaver Burke Model

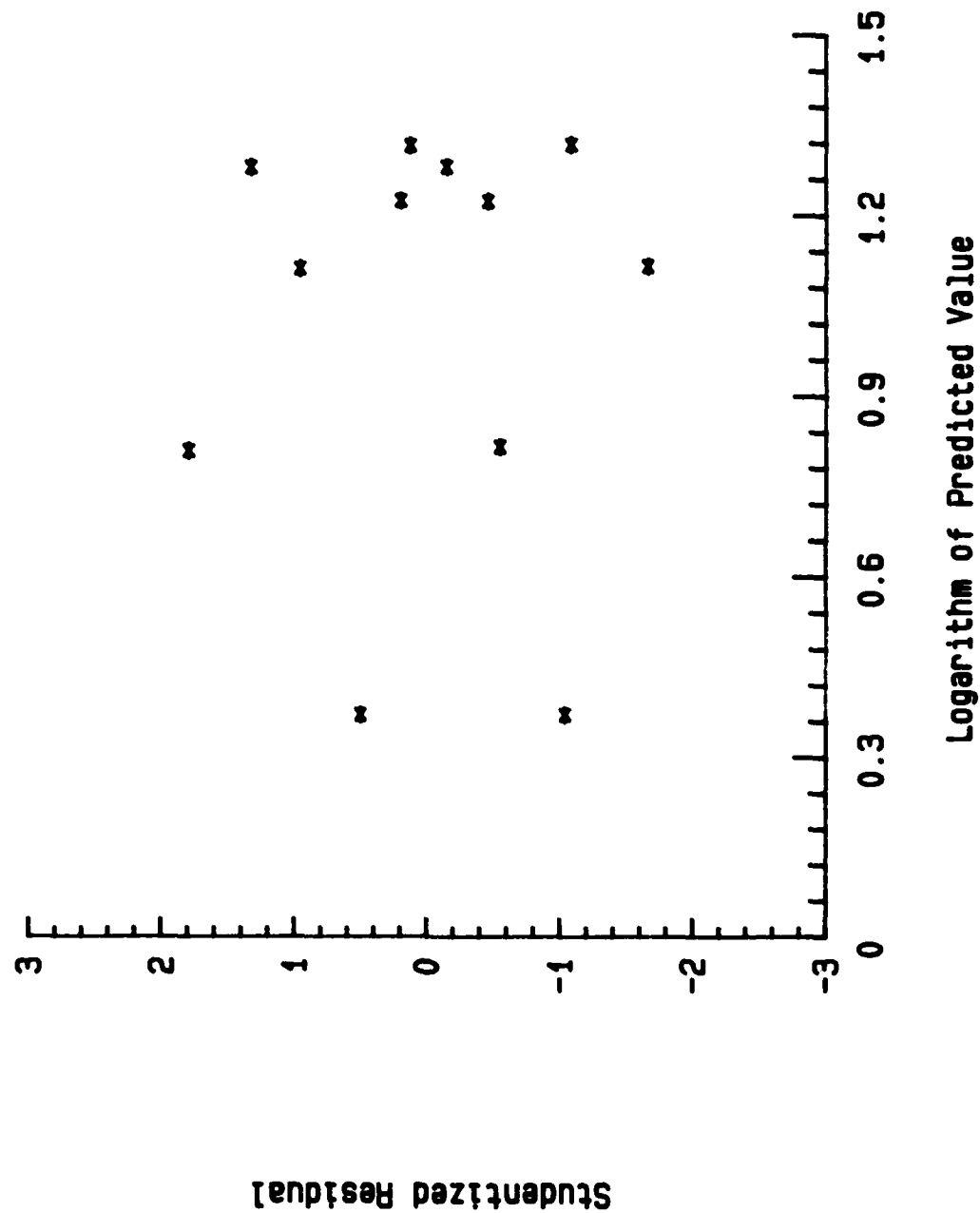


Figure 6

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